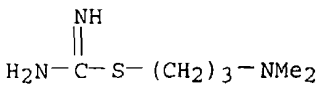
L9 ANSWER 1 OF 1 CAPLUS COPYRIGHT 2003 ACS on STN
AN 1999:272160 CAPLUS
DN 130:307014
TI Histamine H2-receptor modulation in two mouse models of **seizure** susceptibility
AU Seeley, N. A.; Sturman, G.; Meade, H. M.
CS Dep. Life Sci., Univ. East London, London, E15 4LZ, UK
SO Inflammation Research (1999), 48(Suppl. 1), S67-S68
CODEN: INREFB; ISSN: 1023-3830
PB Birkhaeuser Verlag
DT Journal
LA English
CC 2-8 (Mammalian Hormones)
Section cross-reference(s): 1
AB Using dimaprit and zolantidine, histamine H2-receptor modulation was evaluated in 2 mouse **seizure** models (**seizure** chem. induced with leptazol and the DBA/2 mouse strain). Dimaprit (0.3-3 mg/kg) produced a dose-related decrease in the leptazol-**seizure** model in male BK/TO mice with anticonvulsant effects at 0.3, 1, and 3.0 mg/kg in the occurrence of **seizure** incidence. The severity of the **seizures** was also dose-related reduced. In female BK/TO mice, dimaprit (1 mg/kg) increased the leptazol dose needed to evoke tonic **seizures** by .apprx.50%, whereas zolantidine (10 mg/kg) reduced the amt. of leptazol needed to evoke clonic **seizure** in female CD1 mice by >10%. In audiogenic susceptible mice, dimaprit (0.2-3 mg/kg) reduced the **seizure** score of 3.20 in the controls to 2.25, reduced the wild running in the mice, and a difference in respiratory arrest was seen at 1 mg/kg. Zolantidine (3 and 10 mg/kg) increased the **seizure** score of 3.12 in the controls to 4.0. It is concluded that histamine H2-receptor has a modulatory role in epileptic induced **seizures** in mice.
ST dimaprit zolantidine anticonvulsant H2 receptor antagonist
IT Antihistamines
(H2; histamine H2-receptor modulation in 2 mouse models of **seizure** susceptibility)
IT Histamine receptors
RL: BSU (Biological study, unclassified); BIOL (Biological study)
(H2; histamine H2-receptor modulation in 2 mouse models of **seizure** susceptibility)
IT **Epilepsy**
(histamine H2-receptor modulation in 2 mouse models of **seizure** susceptibility)
IT Neurotransmitter agonists
(histaminic H2; histamine H2-receptor modulation in 2 mouse models of **seizure** susceptibility)
IT **65119-89-3**, Dimaprit
RL: BAC (Biological activity or effector, except adverse); BSU (Biological study, unclassified); THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(anticonvulsive activities of dimaprit in mouse models of **seizure** susceptibility)
IT 104076-38-2, Zolantidine
RL: BAC (Biological activity or effector, except adverse); BSU (Biological study, unclassified); THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(pro-convulsant activities of zolantidine in mouse models of **seizure** susceptibility)
RE.CNT 6 THERE ARE 6 CITED REFERENCES AVAILABLE FOR THIS RECORD
RE
(1) Chapman, A; Neurotransmitters and epilepsy 1987, P9
(2) Churchill, J; J Am Med Assoc 1949, V141, P18
(3) De Sarro, G; Gen Pharmacol 1992, V23, P75 CAPLUS
(4) Freeman, P; Br J Pharmacol 1990, V99

(5) Gerald, M; Psychopharmacologia 1976, V46, P277 CAPLUS
(6) Scherkl, R; Epilepsy Res 1991, V10, P111 CAPLUS
IT **65119-89-3**, Dimaprit
RL: BAC (Biological activity or effector, except adverse); BSU (Biological study, unclassified); THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(anticonvulsive activities of dimaprit in mouse models of **seizure** susceptibility)
RN 65119-89-3 CAPLUS
CN Carbamimidothioic acid, 3-(dimethylamino)propyl ester (9CI) (CA INDEX NAME)



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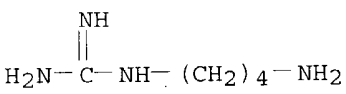
L2 ANSWER 1 OF 1 REGISTRY COPYRIGHT 2004 ACS on STN
RN 306-60-5 REGISTRY
CN Guanidine, (4-aminobutyl)- (8CI, 9CI) (CA INDEX NAME)
OTHER CA INDEX NAMES:
CN **Agmatine (6CI)**
OTHER NAMES:
CN (4-Aminobutyl)guanidine
CN 1,4-Butanediamine, N-(aminoiminomethyl)-
CN 1-Amino-4-guanidinobutane
CN 4-Guanidino-1-butanamine
CN N-(4-Aminobutyl)guanidine
CN NSC 56332
FS 3D CONCORD
MF C5 H14 N4
CI COM
LC STN Files: AGRICOLA, ANABSTR, BEILSTEIN*, BIOBUSINESS, BIOSIS, BIOTECHNO, CA, CABA, CANCERLIT, CAOLD, CAPLUS, CASREACT, CHEMCATS, CHEMLIST, DDFU, DRUGU, EMBASE, IFICDB, IFIPAT, IFIUDB, IPA, MEDLINE, MRCK*, NAPRALERT, PIRA, PROMT, RTECS*, SPECINFO, TOXCENTER, USPAT2, USPATFULL
(*File contains numerically searchable property data)
Other Sources: EINECS**
(**Enter CHEMLIST File for up-to-date regulatory information)



PROPERTY DATA AVAILABLE IN THE 'PROP' FORMAT

998 REFERENCES IN FILE CA (1907 TO DATE)
32 REFERENCES TO NON-SPECIFIC DERIVATIVES IN FILE CA
1002 REFERENCES IN FILE CAPLUS (1907 TO DATE)
44 REFERENCES IN FILE CAOLD (PRIOR TO 1967)

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epilepsy

<disease, neurology> The paroxysmal transient disturbances of brain function that may be manifested as episodic impairment or loss of consciousness, abnormal motor phenomena, psychic or sensory disturbances or perturbation of the autonomic nervous system.

Symptoms are due to paroxysmal disturbance of the electrical activity of the brain. On the basis of origin, epilepsy is idiopathic (cryptogenic, essential, genetic) or symptomatic (acquired, organic). On the basis of clinical and electroencephalographic phenomenon, four subdivisions are recognised:

1. Grand mal epilepsy (major epilepsy, haut mal epilepsy) subgroups: generalised, focal (localised), jacksonian (rolandic)

2. Petit mal epilepsy

3. Psychomotor epilepsy (temporal lobe epilepsy, psychic, psychic equivalent or variant) subgroups: psychomotor proper (tonic with adversive or torsion movements or masticatory phenomena), automatic (with amnesia) and sensory (hallucinations or dream states or d,j. Vu)

4. Autonomic epilepsy (diencephalic), with flushing, pallor, tachycardia, hypertension, perspiration or other visceral symptoms.

Synonym: epilepsia.

Origin: Gr. Epilepsia = seizure

(14 May 1997)

Previous: epilemmal ending, epilepidoma, epilepsia, epilepsia partialis continua
Next: epilepsy, absence, epilepsy, complex partial, epilepsy, frontal lobe

seizure

<clinical sign, neurology> A sudden attack or convulsion due to involuntary electrical activity in the brain. It is due to an uncontrolled burst of electrical activity in the brain that can result in a wide variety of clinical manifestations such as: muscle twitches, staring, tongue biting, urination, loss of consciousness and total body shaking.

Examples include: focal seizure, absence seizure, partial seizure, psychomotor seizure, petit-mal seizure and grand-mal seizures.

(27 Sep 1997)

Previous: seismography, seismological, seismology, seismometer, seismoscope, seismotherapy
Next: seizure, causes of, seizures, sejunction, selachian, selachii

Published at the Dept. of Medical Oncology, University of Newcastle upon Tyne

electroconvulsive

Denoting a convulsive response to an electrical stimulus.

See: electroshock therapy.

(05 Mar 2000)

Previous: electrocochleogram, electrocochleography, electroconductivity, electrocontractility
Next: electroconvulsive therapy, electrocorticogram, electrocorticography

convulsions

Seizures manifested by discontinuous involuntary skeletal muscular contractions, either brief contractions repeated at short intervals or longer ones interrupted by intervals of muscular relaxation.

(12 Dec 1998)

Previous: convolution, convulsant, convulsants, convulsant threshold, convulsion
Next: convulsions, febrile, convulsive, convulsive reflex, convulsive seizure

TITLE: Pharmacomodulation of torasemide led to original diuretic, neuroprotective, anticonvulsant and antithrombotic drugs

AUTHOR(S): Masereel, B.; Dogne, J. M.; Damas, J.; Nuhrich, A.; Varache-Lembege, M.; Fontaine, J.; Pochet, L.; Somers, F.; de Tullio, P.; Pirotte, B.; Delarge, J.

CORPORATE SOURCE: Dep. Medicinal Chem., Univ. Liege, Liege, B-4000, Belg.

SOURCE: Journal de Pharmacie de Belgique (1997), 52(4), 157-158
CODEN: JPBEAJ; ISSN: 0047-2166

PUBLISHER: Masson

DOCUMENT TYPE: Journal

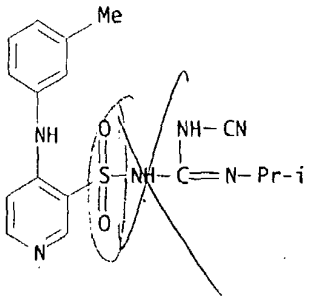
LANGUAGE: English

AB Pharmacomodulation of torasemide, a diuretic sulfonylurea, led to the discovery of two novel diuretics, a sulfonylthiourea (BM 20) and a sulfonylcyanoguanidine (BM 106). BM 27, a lipophilic sulfonylurea, exhibited neuroprotective properties assocd. to an anticonvulsant activity. As BM 27, two lipophilic sulfonylthioureas (BM 11 and BM 34) revealed an anticonvulsant profile similar to that of phenytoin. Finally the synthesis of torasemide derivs. led to the development of a sulfonylcyanoguanidine (BM 144) with a thromboxane A2 antagonist potency.

IT **162586-76-7**, BM 106
RL: BAC (Biological activity or effector, except adverse); BSU (Biological study, unclassified); THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(pharmacomodulation of torasemide led to original diuretic, neuroprotective, **anticonvulsant** and antithrombotic drugs)

RN 162586-76-7 HCAPLUS

CN 3-Pyridinesulfonamide, N-[(cyanoamino)[(1-methylethyl)amino]methylene]-4-[(3-methylphenyl)amino]- (9CI) (CA INDEX NAME)



L60 ANSWER 15 OF 38 HCAPLUS COPYRIGHT 2003 ACS

ACCESSION NUMBER: 1997:376495 HCAPLUS

DOCUMENT NUMBER: 127:93671

TITLE: Effects of the 5-HT3 receptor agonist 1-(m-chlorophenyl)-biguanide in the rat kindling model of epilepsy

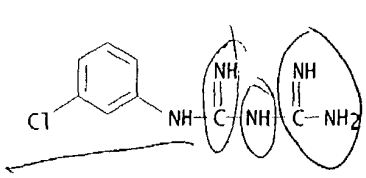
AUTHOR(S): Wada, Yuji; Shiraishi, Jun; Nakamura, Mitsuhiko; Koshino, Yoshifumi

CORPORATE SOURCE: Department of Neuropsychiatry, Kanazawa University School of Medicine, 13-1 Takara-machi, Kanazawa, 920, Japan

SOURCE: Brain Research (1997), 759(2), 313-316
CODEN: BRREAP; ISSN: 0006-8993

PUBLISHER: Elsevier

DOCUMENT TYPE: Journal
LANGUAGE: English
AB This study assessed the action of the serotonin3 (5-HT3) receptor agonist, 1-(m-chlorophenyl)-biguanide (m-CPBG), against both kindled seizures and kindling development from the rat amygdala (AM). The intracerebroventricular (i.c.v.) administration of 40 .mu.g m-CPBG significantly increased the duration of afterdischarge and bilateral forelimb clonus of generalized kindled seizures. In addn., daily i.c.v. treatment with m-CPBG at the same dose prior to each elec. stimulation to the AM significantly facilitated behavioral and electrog. seizure development and reduced the no. of stimulations needed to elicit generalized seizures. The present results indicate that m-CPBG increases the duration of fully kindled seizures and facilitates the developmental seizure process, suggesting an excitatory role of 5-HT3 receptors in the kindling model of epilepsy.
IT **92503-73-6**
RL: BAC (Biological activity or effector, except adverse); BSU (Biological study, unclassified); BIOL (Biological study)
(effects of 5-HT3 receptor agonist (chlorophenyl)biguanide in kindling model of **epilepsy**)
RN 92503-73-6 HCAPLUS
CN Imidodicarbonimidic diamide, N-(3-chlorophenyl)-, hydrochloride (9CI) (CA INDEX NAME)



●x HCl

L60 ANSWER 16 OF 38 HCAPLUS COPYRIGHT 2003 ACS
ACCESSION NUMBER: 1996:430360 HCAPLUS
DOCUMENT NUMBER: 125:137120
TITLE: Quantitation of the putative neurotransmitter agmatine as the hexafluoroacetylacetonate derivative by stable isotope dilution gas chromatography and negative-ion chemical ionization mass spectrometry
AUTHOR(S): Stickle, Douglas; Bohrer, Alan; Berger, Richard; Morrissey, Jeremiah; Klahr, Saulo; Turk, John
CORPORATE SOURCE: Mass Spectrometry Resource Div. Lab. Med., Washington Univ. Sch. Med., St. Louis, MO, 63110, USA
SOURCE: Analytical Biochemistry (1996), 238(2), 129-136
CODEN: ANBCA2; ISSN: 0003-2697
PUBLISHER: Academic
DOCUMENT TYPE: Journal
LANGUAGE: English
AB A method is described for detection and quantitation of agmatine [4-(aminobutyl)guanidine] by gas chromatog./neg.-ion chem.-ionization/mass spectrometry after derivatization with hexafluoroacetylacetone. The lower limit of detection of the deriv. was about 25 fmol on-column. For quant. studies of agmatine content in biol. samples, a procedure utilizing an internal std. ([15N4]agmatine prepd. from [15N4]arginine) and an extn. step had a lower limit of detection of about 15 pmol for total sample content. Agmatine content was measured in rat tissue samples and

SG, SI, SK, SL, TJ, TM, TR, TT, TZ, UA, UG, US, UZ, VN, YU, ZA, ZW, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM
RW: GH, GM, KE, LS, MW, SD, SL, SZ, TZ, UG, ZW, AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE, BF, BJ, CF, CG, CI, CM, GA, GN, GW, ML, MR, NE, SN, TD, TG

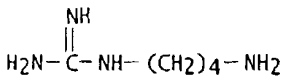
FR 2791571	A1	20001006	FR 1999-4134	19990402
FR 2791571	B1	20021004		
EP 1169005	A2	20020109	EP 2000-915262	20000331
R: AT, BE, CH, DE, DK, ES, FR, GB, GR, IT, LI, LU, NL, SE, MC, PT, IE, SI, LT, LV, FI, RO				
NO 2001004770	A	20011123	NO 2001-4770	20011001

PRIORITY APPLN. INFO.: FR 1999-4134 A 19990402
WO 2000-FR812 W 20000331

AB The invention relates to a pharmaceutical compn. comprising as an active ingredient one or several substances interfering with the synthesis of nitrogen monoxide by inhibiting NO-synthase and one or several metabolic antioxidants contg. thiol groups and intervening in the redox status of the thiol groups, and optionally a pharmaceutically acceptable support. The invention also relates to a product contg. one or several NO-synthase inhibitors and one or several metabolic antioxidants intervening in the redox status of the thiol groups, as a combined product in a sepd. form of said active ingredients. A mixt. of 3 mg/kg N-phenyl-2-thiophenecarboximidamine and 10 mg/kg lipoic acid increased the dopamine level in guinea pigs suffering from parkinson to 5.21 ng/mg nervous tissue which was higher than either compds.

IT **306-60-5**, Agmatine
RL: BAC (Biological activity or effector, except adverse); BSU (Biological study, unclassified); THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(assocn. of NO-synthase inhibitors and metabolic antioxidants)

RN 306-60-5 HCAPLUS
CN Guanidine, (4-aminobutyl)- (8CI, 9CI) (CA INDEX NAME)



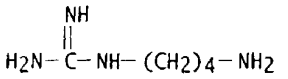
L60 ANSWER 10 OF 38 HCAPLUS COPYRIGHT 2003 ACS
ACCESSION NUMBER: 1999:762300 HCAPLUS
DOCUMENT NUMBER: 132:202985
TITLE: Effects of agmatine on ethanol withdrawal syndrome in rats
AUTHOR(S): Uzbay, I. T.; Yesilyurt, O.; Celik, T.; Ergun, H.; Isimer, A.
CORPORATE SOURCE: Faculty of Medicine, Psychopharmacology Research Unit, Department of Medical Pharmacology, Gulhane Military Medical Academy, Etlik, Ankara, 06018, Turk.
SOURCE: Behavioural Brain Research (2000), 107(1,2), 153-159
CODEN: BBREDI; ISSN: 0166-4328
PUBLISHER: Elsevier Science Ireland Ltd.
DOCUMENT TYPE: Journal
LANGUAGE: English

AB Effects of agmatine, which is an endogenous polyamine metabolite formed by decarboxylation of L-arginine, have been investigated on the ethanol withdrawal syndrome in rats. Adult male Wistar rats were used in the study. Ethanol (7.2% vol./vol.) was given to the rats by a liq. diet for 21 days. Agmatine (20, 40, 80 and 160 mg/kg) and saline were injected to

rats i.p. 30 min before ethanol withdrawal testing. After 30th min, 2nd and 6th h of ethanol withdrawal, rats were obsd. for 5 min, and withdrawal signs which included locomotor hyperactivity, agitation, stereotyped behavior, wet dog shakes and tremor were recorded or rated. A second series of injections was given at 6 h after the first one, and subjects were then tested for audiogenic **seizures**. Agmatine caused dose-dependent and significant inhibitory effects on stereotyped behaviors, wet dog shakes and tremors during the observation period. It did not cause any significant change in motor coordination of naive (not ethanol-dependent) rats. The authors' results suggest that agmatine attenuates withdrawal syndrome in ethanol-dependent rats; thus, this drug may be beneficial in the treatment of ethanol dependence.

IT **306-60-5**, Agmatine
RL: BAC (Biological activity or effector, except adverse); BSU (Biological study, unclassified); THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(agmatine effects on ethanol withdrawal syndrome in rats)

RN 306-60-5 HCAPLUS
CN Guanidine, (4-aminobutyl)- (8CI, 9CI) (CA INDEX NAME)



REFERENCE COUNT: 46 THERE ARE 46 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L60 ANSWER 11 OF 38 HCAPLUS COPYRIGHT 2003 ACS
ACCESSION NUMBER: 1999:272160 HCAPLUS
DOCUMENT NUMBER: 130:307014
TITLE: Histamine H2-receptor modulation in two mouse models of seizure susceptibility
AUTHOR(S): Seeley, N. A.; Sturman, G.; Meade, H. M.
CORPORATE SOURCE: Dep. Life Sci., Univ. East London, London, E15 4LZ, UK
SOURCE: Inflammation Research (1999), 48(Suppl. 1), S67-S68
CODEN: INREFB; ISSN: 1023-3830
PUBLISHER: Birkhaeuser Verlag
DOCUMENT TYPE: Journal
LANGUAGE: English

AB Using dimaprit and zolantidine, histamine H2-receptor modulation was evaluated in 2 mouse seizure models (seizure chem. induced with leptazol and the DBA/2 mouse strain). Dimaprit (0.3-3 mg/kg) produced a dose-related decrease in the leptazol-seizure model in male BK/TO mice with anticonvulsant effects at 0.3, 1, and 3.0 mg/kg in the occurrence of seizure incidence. The severity of the seizures was also dose-related reduced. In female BK/TO mice, dimaprit (1 mg/kg) increased the leptazol dose needed to evoke tonic seizures by .apprx.50%, whereas zolantidine (10 mg/kg) reduced the amt. of leptazol needed to evoke clonic seizure in female CD1 mice by >10%. In audiogenic susceptible mice, dimaprit (0.2-3 mg/kg) reduced the seizure score of 3.20 in the controls to 2.25, reduced the wild running in the mice, and a difference in respiratory arrest was seen at 1 mg/kg. Zolantidine (3 and 10 mg/kg) increased the seizure score of 3.12 in the controls to 4.0. It is concluded that histamine H2-receptor has a modulatory role in epileptic induced seizures in mice.

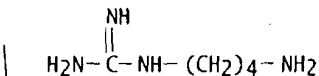
IT **65119-89-3**, Dimaprit
RL: BAC (Biological activity or effector, except adverse); BSU (Biological study, unclassified); THU (Therapeutic use); BIOL (Biological study); USES (Uses)

normalized to protein content. Kidney and spleen samples exhibited the greatest content of agmatine per unit protein mass but agmatine was also detected in pancreatic islets and brain regions (cerebellum and cerebral cortex). On the basis of these measurements, it is estd. that the pancreatic islet intracellular agmatine concn. may exceed 1 .mu.M. The sensitive and highly specific means of detection and quantitation provided by mass spectrometry may be useful in investigating the physiol. role of agmatine in mammalian systems.

IT **306-60-5DP**, Agmatine, hexafluoroacetylacetone conjugates
RL: ARG (Analytical reagent use); SPN (Synthetic preparation); ANST (Analytical study); PREP (Preparation); USES (Uses)
(putative neurotransmitter agmatine detn. as hexafluoroacetylacetonate deriv. by gas chromatog./ mass spectrometry)

RN 306-60-5 HCAPLUS

CN Guanidine, (4-aminobutyl)- (8CI, 9CI) (CA INDEX NAME)



L60 ANSWER 17 OF 38 HCAPLUS COPYRIGHT 2003 ACS

ACCESSION NUMBER: 1995:206613 HCAPLUS

DOCUMENT NUMBER: 122:6277

TITLE: Structure-activity relationships of arginine analogs on nitric oxide synthase activity in the rat brain

AUTHOR(S): Yokoi, I.; Kabuto, H.; Habu, H.; Inada, K.; Toma, J.; Mori, A.

CORPORATE SOURCE: Inst. Mol. Cellular Medicine, Okayama Univ. Med. School, Okayama, 700, Japan

SOURCE: Neuropharmacology (1994), 33(11), 1261-5
CODEN: NEPHBW; ISSN: 0028-3908

PUBLISHER: Elsevier

DOCUMENT TYPE: Journal

LANGUAGE: English

AB Nitric oxide (NO) is synthesized by nitric oxide synthase (NOS) from L-arginine (Arg) which as a guanidino group in its mol. We examd. the effect of 23 different Arg analogs on NOS activity in the rat brain. Though homoarginine, .epsilon.-guanidinocaproic acid and canavanine act as substrates of NOS, prodn. of NO from them was lower than that from Arg. .alpha.-Guanidinoglutaric acid (2-GGA) and arcaine inhibited NOS activity at levels equal to NG-monomethyl-L-arginine (MeArg), a well known NOS inhibitor. Though almost all previously reported NOS inhibitors were synthesized by substituting the guanidino nitrogen of Arg, the guanidino nitrogens of arcaine and 2-GGA were not substituted. Furthermore, 2-GGA is a known endogenous **convulsant** in mammals, and arcaine, which was isolated from a marine mollusc, is also a **convulsive** substance. Hence, 2-GGA and arcaine will be excellent drugs to investigate not only the chem. nature of NOS but also the physiol. function of NO.

IT **306-60-5**, Agmatine
RL: BAC (Biological activity or effector, except adverse); BSU (Biological study, unclassified); BIOL (Biological study)
(structure-activity relationships of arginine analogs on nitric oxide synthase activity in brain)

RN 306-60-5 HCAPLUS

CN Guanidine, (4-aminobutyl)- (8CI, 9CI) (CA INDEX NAME)

INTERNAT SEARCH REPORT

International application No.
PCT/US01/19095

A. CLASSIFICATION OF SUBJECT MATTER
IPC(7) :A61K 31/155
US CL :514/634
According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)
U.S. : 514/634

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practicable, search terms used)

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X, P ---- A, P	US 6,150,419 A (FAIRBANKS et al.) 21 November 2000 (21.11.00), see the entire document.	1-4 ---- 5-20
X ---- A	US 5,677,349 A (GILAD et al.) 14 October 1997 (14.10.97), see the entire document, especially column 3, lines 23-36.	1-4 ---- 5-20

☐ Further documents are listed in the continuation of Box C. ☐ See patent family annex.

*	Special categories of cited documents:	"T"	later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention
"A"	document defining the general state of the art which is not considered to be of particular relevance	"X"	document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone
"E"	earlier document published on or after the international filing date	"Y"	document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art
"L"	document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)	"&"	document member of the same patent family
"O"	document referring to an oral disclosure, use, exhibition or other means		
"P"	document published prior to the international filing date but later than the priority date claimed		

Date of the actual completion of the international search
03 AUGUST 2001

Date of mailing of the international search report
02 OCT 2001

Name and mailing address of the ISA/US
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Authorized officer
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Telephone No. (703) 308-1235

Form PCT/ISA/210 (second sheet) (July 1998)*

L31 ANSWER 3 OF 5 EMBASE COPYRIGHT 2004 ELSEVIER INC. ALL RIGHTS RESERVED. on STN

AN 2003315014 EMBASE

TI Agmatine exerts anticonvulsant effect in mice: Modulation by α(2)-adrenoceptors and nitric oxide.

AU Demehri S.; Homayoun H.; Honar H.; Riazi K.; Vafaie K.; Roushanzamir F.; Dehpour A.R.

CS A.R. Dehpour, Department of Pharmacology, School of Medicine, Tehran Univ. of Medical Sciences, P.O. Box 13145-784, Tehran, Iran (Islamic Republic of). dehpour@medscape.com

SO Neuropharmacology, (2003) 45/4 (534-542).
Refs: 52
ISSN: 0028-3908 CODEN: NEPHBW

CY United Kingdom

DT Journal; Article

FS 008 Neurology and Neurosurgery
030 Pharmacology
037 Drug Literature Index

LA English

SL English

AB The effect of **agmatine**, an endogenous polyamine metabolite, on **seizure** susceptibility was investigated in mice. Acute intraperitoneal administration of **agmatine** (5, 10, 20, 40 mg/kg) had a significant and dose-dependent inhibitory effect on pentylenetetrazole (PTZ)-induced **seizures**. The peak of this anticonvulsant effect was 45 min after **agmatine** administration. We further investigated the possible involvement of the α(2)-adrenoceptors and L-arginine/NO pathway in this effect of agmatine. The α(2)-adrenoceptor antagonist, yohimbine (0.5-2 mg/kg), induced a dose-dependent blockade of the anticonvulsant effect of agmatine. The nitric oxide synthase (NOS) substrate, L-arginine (60 mg/kg), inhibited the anticonvulsant property of agmatine and this effect was significantly reversed by NOS inhibitor N(G)-nitro-L-arginine (L-NAME, 30 mg/kg), implying an NO-dependent mechanism for L-arginine effect. We further examined a possible additive effect between agmatine (1 or 5 mg/kg) and L-NAME (10 mg/kg). The combination of L-NAME (10 mg/kg) with **agmatine** (5 but not 1 mg/kg) induced a significantly higher level of **seizure** protection as compared with each drug alone. Moreover, a combination of lower doses of yohimbine (0.5 mg/kg) and L-arginine (30 mg/kg) also significantly decreased the anticonvulsant effect of **agmatine**. In conclusion, the present data suggest that **agmatine** may be of potential use in **seizure** treatment.

CT Medical Descriptors:
*anticonvulsant activity
*neuromodulation
seizure susceptibility
signal transduction
dose response
drug effect
drug antagonism
drug potentiation
drug potency
brain protection
nonhuman
male
mouse
animal experiment
animal model
controlled study
article
priority journal
Drug Descriptors:

*agmatine: DO, drug dose
*agmatine: PD, pharmacology
*agmatine: IP, intraperitoneal drug administration
*alpha 2 adrenergic receptor: EC, endogenous compound
*nitric oxide: EC, endogenous compound
arginine: EC, endogenous compound
yohimbine: DO, drug dose
yohimbine: PD, pharmacology
alpha adrenergic receptor blocking agent: DO, drug dose
alpha adrenergic receptor blocking agent: PD, pharmacology
nitric oxide synthase inhibitor: PD, pharmacology
n(g) nitroarginine methyl ester: PD, pharmacology
nitric oxide synthase: PD, pharmacology
pentetrazole

RN (agmatine) 306-60-5; (nitric oxide) 10102-43-9; (arginine) 1119-34-2, 15595-35-4, 7004-12-8, 74-79-3; (yohimbine) 146-48-5, 65-19-0; (n(g) nitroarginine methyl ester) 50903-99-6; (nitric oxide synthase) 125978-95-2; (pentetrazole) 54-95-5

CO Sigma (United Kingdom)

IT 50-53-3, Phenothiazine, 2-chloro-10-[3-(dimethylamino)propyl]- 54-04-6, Phenethylamine, 3,4,5-trimethoxy- 57-41-0, Hydantoin, 5,5-diphenyl- 59-47-2, 1,2-Propanediol, 3-(o-tolyloxy)- 7647-15-6, Sodium bromide
(convulsions (**audiogenic**) in relation to)

IT 113-15-5, Ergotamine 300-62-9, Phenethylamine, α-methyl- 7562-87-0, Ammonium, (2-hydroxypropyl)trimethyl
(convulsions (**audiogenic**) response to)

IT 58-08-2, Caffeine 76-22-2, Camphor
(convulsions from)

IT 3865-10-9, Barbituric acid, 5-(m-bromophenyl)-5-ethyl-
(effect on convulsions (**audiogenic**))

IT 7440-23-5, Sodium
(in blood, **audiogenic** convulsions and)

IT 51-55-8, Atropine
(in convulsion (**audiogenic**))

IT 124-87-8, Picrotoxin
(in convulsion (**audiogenic**) induction)

L5 ANSWER 72 OF 163 CAPLUS COPYRIGHT 2004 ACS on STN
AN 1964:413971 CAPLUS
DN 61:13971
OREF 61:2355h,2356a-c
ED Entered STN: 22 Apr 2001
TI Modification of **audiogenic** crisis in albino rats by the influence of various pharmacodynamic agents
AU Mercier, J.
CS Fac. Med., Marseilles, Fr.
SO Colloques Internationaux du Centre National de la Recherche Scientifique (1963), No. 112, 331-84, discussion 385-92
CODEN: COINAV; ISSN: 0366-7634
DT Journal
LA Unavailable
CC 68 (Pharmacodynamics)
AB Animals used were albino rats bred to have a high incidence of **seizures** when exposed to a standard sound. The incidence of **seizures** could be lowered by previously administering barbiturates, hydantoins, and oxazolidinediones. For example, diphenylhydantoin at 25 mg./kg. was 100% effective as a protectant, as was phenobarbital at 4 mg./kg., and trimethyloxazolidinedione at 300 mg./kg. Some protection was afforded by Gardenal, the m-Br derivative of Gardenal, NaBr, hypnotics such as chloral and barbital, central-acting agents such as morphine and dihydrooxycodenone-HCl, local anesthetics such as cocaine-HCl, Delcaine, and procaine, neuroplegics such as chlorpromazine, and medullary depressants such as 3-o-tolyloxy-1,2-propanediol. Drugs acting on the autonomic nervous system offered some protection (atropine, eserine, mecholyl, epinephrine, ephedrine, amphetamine), as did alkaloids and miscellaneous agents (yohimbine, ergotamine, papaverine, and others). The wide variety of effective drugs speaks against **audiogenic** **seizure** being an **epileptic** manifestation. It was possible to induce **seizure** in otherwise nonsensitive animals pretreated with convulsants (caffeine 50- 100 mg./kg., theophylline 100-150 mg./kg., camphor oil 50-100 mg./kg., picrotoxin 2 mg./kg.). Hyponatremia induced by intraperitoneal isotonic glucose (100 ml./kg.) afforded some protection. Some neurostimulants such as epinephrine and its analogs offered protection. Mecholyl, acetylcholine, and neostigmine were unable to induce **seizure** in nonsensitive animals.
IT Convulsions (spasms)
(effect of alkaloids, anesthetics, hypnotics, etc., on **audiogenic**)
IT Blood
(sodium in, **audiogenic** convulsion and)
IT 50-06-6, Barbituric acid, 5-ethyl-5-phenyl-
(antispasmodic acitivity of)
IT 124-90-3, Codeinone, dihydro-14-hydroxy-, hydrochloride
(**audiogenic** convulsions in relation to)
IT 58-55-9, Theophylline
(convulsion (**audiogenic**) induction and)
IT 50-36-2, Cocaine 57-27-2, Morphine 58-74-2, Papaverine 146-48-5, Yohimbine 329-65-7, Benzyl alcohol, 3,4-dihydroxy-α-[(methylamino)methyl]- 442-51-3, Harmine 478-73-9, Pseudococaine
(convulsion (**audiogenic**) response to)
IT 299-42-3, Ephedrine
(convulsion from sound response to)
IT 50-06-6, Barbituric acid, 5-ethyl-5-phenyl- 57-44-3, Barbituric acid, 5,5-diethyl- 59-46-1, Benzoic acid, p-amino-, 2-(diethylamino)ethyl ester
(convulsion response to)
IT 127-48-0, 2,4-Oxazolidinedione, 3,5,5-trimethyl-
(convulsion response to **audiogenic**)
IT 75-87-6, Chloral
(convulsions (**audiogenic**) and)

L5 ANSWER 73 OF 163 CAPLUS COPYRIGHT 2004 ACS on STN
AN 1960:51611 CAPLUS
DN 54:51611
OREF 54:10161g-h
ED Entered STN: 22 Apr 2001
TI The effect of some antiepileptic drugs on **audiogenic epileptic seizures** and conditioned reflex activity in the rat
AU Chocholova, L.
CS Physiol. Inst., CsAV, Prague
SO Physiologia Bohemoslovenica (1956-65) (1959), 8, 422-30
CODEN: PHBOAP; ISSN: 0031-9309
DT Journal
LA English
CC 11H (Biological Chemistry: Pharmacology)
AB Repeated oral administration of diphenylhydantoin, triantoin (mesantoin), and phenacemide (I) decreased the frequency of **audiogenic epileptic seizures** in slightly susceptible rats. No changes in conditioned reflex activity were observed with repeated administration in anticonvulsant dosages of I to nonconvulsant rats.
IT Convulsions
(from sound, effect of 5,5-diphenylhydantoin, 5-ethyl-3-methyl-5-phenylhydantoin and (phenylacetyl)urea on)
IT 50-12-4, Hydantoin, 5-ethyl-3-methyl-5-phenyl- 57-41-0, Hydantoin, 5,5-diphenyl- 63-98-9, Phenacemide
(effect on convulsions)

=>

L15 ANSWER 5 OF 5 USPATFULL on STN

SUMM The biosyntheses of putrescine, spermidine and spermine are interrelated. Putrescine is the decarboxylation product of ornithine, catalyzed by ornithine decarboxylase. Putrescine formation may also occur by decarboxylation of arginine to form **agmatine** which is hydrolyzed to give putrescine and urea. Arginine is also involved in ornithine formation by action of the enzyme arginase. Activation of methionine by S-adenosylmethionine synthetase forms S-adenosylmethionine which is decarboxylated, after which the propylamine moiety of activated methionine may be transferred to putrescine to form spermidine or the polyamine moiety may be transferred to spermidine to form spermine. Hence, putrescine serves as a precursor to spermidine and spermine and additionally has been shown to have a marked regulatory effect upon the polyamine biosynthetic pathway in that it has been shown that increased synthesis of putrescine is the first indication that a tissue will undergo renewed growth processes. Cadaverine which is the decarboxylation product of lysine has been shown to stimulate the activity of S-adenoxylmethionine decarboxylase and is known to be essential to growth processes of many microorganisms, for example, H. parainfluenza.

SUMM The compounds of general Formula I wherein Z is ##STR18## wherein n is the integer 2 or 3 and R.sub.1 is hydrogen are metabolic precursors of compounds of the following structure ##STR19## wherein n is the integer 2 or 3 and Y has the meaning defined in Formula I which are known to be irreversible inhibitors of γ-aminobutyric acid transaminase and upon administration results in higher brain levels of γ-aminobutyric acid (GABA). As precursors of γ-mono, di or tri-fluoromethyl β-aminobutyric acid the above-described compounds of Formula I are useful in the treatment of disorders of the central nervous system consisting of involuntary movement associated with Huntington's chorea, Parkinsonism, extrapyramidal effects of drugs, for example, neuroleptic **seizure** disorders associated with **epilepsy**, alcohol withdrawal, psychoses associated with schizophrenia, depression, manic depression and hyperkinesis.

ACCESSION NUMBER:	79:3175 USPATFULL
TITLE:	Alpha-halomethyl derivatives of amines
INVENTOR(S):	Bey, Philippe, Strasbourg, France Jung, Michel, Illkirch Graffenstaden, France
PATENT ASSIGNEE(S):	Merrell Toraude et Compagnie, Strasbourg, France (non-U.S. corporation)

	NUMBER	KIND	DATE	
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PRIMARY EXAMINER:	Douglas, Winston A.
ASSISTANT EXAMINER:	Doll, John
LEGAL REPRESENTATIVE:	Hattan, L. Ruth, Retter, Eugene O., Rauchfuss, Jr., George W.
NUMBER OF CLAIMS:	10
EXEMPLARY CLAIM:	1
LINE COUNT:	1181

CAS INDEXING IS AVAILABLE FOR THIS PATENT.